Message

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Sent: 2/3/2016 1:27:42 PM
To: Thomas, Russell [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=12f119e7a3ee447499f3d6ab5d20daeb-Thomas, Rus]
Subject: Regulatory authority use of ToxCast data: criteria for consideration
Attachments: PMRA_K P Friedman.pptx

Hi Rusty,

Over the last 1-2 years one of the issues I have often grappled with is industry's concern over "misuse" of publicly-available ToxCast data (i.e., inappropriate matching of the data to the level of decision-making). I have a paper in review at Critical Reviews in Tox right now where we try to illustrate what we view as a great use of these kind of data using an endocrine prioritization example. A month or two ago I was made aware of IARC's intention to possibly use ToxCast data in categorization of carcinogens, and last year I reviewed a preliminary document showing JRC's intention to use ToxCast data in the endocrine disruptor impact assessments being conducted in order to finalize ED classification and labeling criteria in the EU. Both of these nascent efforts seemed to mismatch the level of data certainty with the level/impact of decision, and neither appeared to appropriately outline how one might consider ToxCast data on a single chemical basis.

In reality, of course, the current iteration of ToxCast as a biochemical and cell-based assay suite was not really designed for the assessment of single chemicals; rather, the power of these data were in prioritization of lists of chemicals, and in potential learning of the "fingerprint" of chemicals that might impact in vivo rodent/rabbit biology. And this is very valuable and fits the level of decisionmaking (largely prioritization, in conjunction with predicted exposure ranges) that was initially intended. Of course moving to a "Tier 0" that includes a global transcriptomic approach will have new challenges and new opportunities for single chemicals; indeed, I think a more global approach like this might have more relevance for a group like IARC. However, we are still left with a very short-term yet important issue: how to provide an appropriate guide for considering the value of ToxCast/Tox21 data on a single chemical basis for previously registered molecules. Because these data are available to regulatory authorities, particularly those outside the US, this is a very present concern.

Last week I discussed with Rick Becker at ACC an idea I've been using internally here and have been kicking around with external colleagues for awhile: the concept of some sort of modified Bradford Hill set of questions to consider the available ToxCast/Tox21 data in order to make sure the appropriate level of confidence is assigned to these data – at this current stage of the program. Of course you could imagine simply modifying criteria like these for any publicly available data set. Rick thought that a white paper (or maybe a publication?) might be appropriate to address this near-term issue (ED impact assessments are supposed to come out in Q2 so this might not be proactive for that – but better than never considering our ongoing Annex I renewal schedules for chemicals in Europe). This might be something we could include as an appendix to our submissions in the EU. My management would prefer a peer-reviewed publication, but in general we want to get something out that can be used, referenced, etc.

I'd like to get your feedback on this and perhaps have a longer conversation about how you might view some work to try to promote use of these data while cautioning against their "misuse," particularly in geographies with bans/cut-off criteria for classification and labeling. We want to support predictive toxicology at EPA, and the immense efforts put into transparency and data-sharing, while developing a scientifically-credible approach to handling these information. As an example, you can imagine the danger of a regulatory authority doing some like looking at some positive hitcalls in ER-related assays, and not realizing these should be viewed in the context of the ER pathway model, which might be negative (check out bromoxynil as an example of this – and note that this is just one example chemical for which a regulatory authority asked us about the ToxCast data for this chemical).

I understand there may be limits to what EPA ORD can do to provide guidance to the public, particularly international regulatory authorities, at different points in time regarding use of ToxCast data. But perhaps this is something we can do together, or at least in some kind of informative partnership, so that the true strengths of ToxCast and optimal use can be highlighted – this seems to me the best way to promote incremental acceptance of technology and progress.

Please let me know what you think about a white paper or similar effort at ACC, and if you'd like to have a call or chat in person. A rough idea (below) and a short presentation made at PMRA last year about an example is attached. Thank you.

#	Criterion	Corresponding questions of high-throughput assays

1	Temporal	Q1	Do nonselective toxicities, including oxidative stress and cytotoxicity among others, precede assay predictions for endocrine activity?
2	Strength	Q2	Is the assay effect statistically significant, biologically significant, both, neither, or indeterminate?
		Q3	How does the magnitude of the in vitro effect (efficacy) compare to the in vitro effect of reference chemicals that interact with the endocrine system?
3	Dose-Response	Q4	Does increasing assay concentration correspond to increasing assay effect in the absence of cytoxicity or solubility artifacts?
		Q5	Is the assay concentration range relevant to the in vivo exposure range for (1) safety testing in animals, and/or (2) the human population?
		Q6	How does the potency of a chemical with efficacy in this assay compare with a reference chemical potency?
4	Consistency	Q6	What is the "read-across" for assays that assess the same target (orthogonal assays)?
		Q7	What is the read-across for assays that assess related targets?
		Q8	What is the read-across for high-throughput assays that assess related key events?
5	Plausibility	Q9	Is there confidence that the key event assessed by this assay is necessary for development of an adverse outcome (AO)?
		Q10	How well is the adverse outcome pathway (AOP) characterized for the key event assessed by this assay?
6	Specificity	Q11	How well does this assay mimic a known in vivo key event?
		Q12	Is the assay vulnerable to confounding factors, and can these confounders be isolated?
		Q13	Does this assay measure one event, or are other possible events also indicated by this signal?
7	Coherence	Q14	What is the correspondence to known in vivo data for this chemical?
		Q15	Is there a predictive model for an adverse outcome that includes this assay or set of assays?
8	Other factors/ alternate explanation	Q16	Is metabolism critical to the presence/absence of an effect for a specific chemical, and does this assay include metabolic function?
		Q17	Are there interspecies differences that may be critical to interpreting the effect or lack of effect in this assay?
		Q18	Are there differences in life-stage susceptibility involved in mediating the anticipated adverse outcome, and does this assay provide assessment of these differences?
		Q19	Are there alternate AOPs that could contribute to the adverse outcome under consideration, and are high-throughput data available to assess this alternate AOP?

Kind regards,

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